



A STORY ABOUT GENDER

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Introduction

Insight

Our society is practically built on the difference between men and women. The first thing people ask when a baby is born is: 'Is it a girl or a boy?'. People organize baby showers to reveal the gender of the unborn baby and it does not stop there. Whether you sign up for a Facebook account, apply for a job or subscribe to a magazine, one of the first questions to be asked about is your gender. However, this distinct division between genders is fading.

A few weeks ago, the common broadcast: "Good evening ladies and gentlemen," as heard often by commuters by train, was changed to "Good evening travellers" by the Dutch railway company Nederlandse Spoorwegen (NS) [1]. This change was accompanied with much ado and even made it to the headlines, but why? By addressing travellers in this new manner, the railway company supports the statement that people should not be limited to the binomial concept of gender. The concept of sexes, which seemed obvious before, has now become subject of debate. To most people, identifying as a male or female is self-evident, but this is not the case for people who are intersexual, bigender or transgender. To be able to address all travellers, the NS chooses this gender neutral approach.

While this Dutch company was worried about insulting anyone by addressing them with gender specific greetings, a different problem regarding the subject of gender has arisen as President Trump has banned transgender people from serving in the military. According to Trump, transgenderism in the military is accompanied by 'tremendous medical costs' and 'disruption of the military' [2]. These two very opposite but substantial discussions about gender differentiation show the relevance of this topic.

The distinction between sexes seems clear, but this is not the case for everyone. How is it possible that something that seems so obvious can be so confusing? Why do some people feel like they should be part of the opposite gender or identify themselves as both male and female? In what way are transgenders, people whose gender identity does not match the sex they were assigned at birth, different from cisgenders, people whose gender identity does match the sex that they were assigned at birth? With this article, we hope to shed some light on the gender division by looking at three possible factors that could play a role in transgenderism: neuroanatomical, hormonal and environmental factors.

Neuroanatomical differences between genders

It has been speculated that the gender identity of a person is associated with certain structures in the brain. Many studies show that the brains of male-to-female transsexuals, so called trans women, are more like the brains of cis women's and less like cis men's or represent an intermediate form. One of the first studies that has been published concerning transsexuality studied potential volume differences between genders of the central part of the bed nucleus of the stria terminalis (BSTc) [3]. The stria terminalis is a brain structure that connects, amongst others, the amygdala and the hypothalamus. Noteworthy, this brain region contains important sex hormones such as androgen and oestrogen receptors. The size of the BSTc was found to be about 44% greater in cis men compared to cis women. The size of the BSTc of male-to-female transsexuals laid within the range of those of cis women and appeared

to be independent of sexual orientation and sex hormone levels. A subsequent follow-up study focused on the number of neurons in the BSTc in various male, female and transgender brains and the previous finding of neuroanatomical gender differences was confirmed [4]. Moreover, the number of neurons in trans women was found to be similar to that in cis women and the number of trans men lay in the range of the cis men's number. Even more, the number of neurons was also independent of sex hormones, suggesting that hormone treatment does not affect neuron numbers and is therefore not responsible for the observed differences in brain structure. This indicates that these differences had to be established earlier during brain development. These differences are confirmed to become apparent later in an individual's life by Chung et al. [5].

Chung et al. aimed to clarify at what stage in life the differences in brain structure between men and women become apparent. BSTc volume and neuronal density were determined in human brain tissue from males and females residing in one of the following categories: fetuses or neonates, infants or adolescents, and adults. The volume of the BSTc increased with age in both males and females, but the sex differences in BSTc volume only became statistically significant in adulthood, which means that the BSTc volume in neonates, infants and adolescents are similar, independent of gender. However, the finding that sex differences of the BSTc occur later in life conflicts with the experience of many transgenders who often feel from childhood onwards that they have been born in the wrong body. This could suggest that sex differences in brain structure are not the cause of transsexuality. Yet, it is possible that the cause of transsexuality is determined very early in life and that this also has an effect on the structure of the BSTc later in life. For instance, the authors speculate that the most likely cause of the observed sex differences in brain structures are prenatal or neonatal androgens and estrogens levels. This speculation suggests that hormone levels early in life dictate the sexual differentiation of the brain, whereas hormone levels in puberty and throughout life are responsible for the sexual differentiation of the body. This could mean that both transsexuality and the differentiation in brain structure are consequences of hormone levels early in life or another unknown process. The same and other research groups found sex differences in other brain structures as well, such as the thalamus, midbrain and gyrus precentralis [6,7]. It remains unclear how and when these differences in brain structure develop and whether these are the cause of transsexuality or the result of some other unknown mechanism responsible for transgender people to feel they have been born in the wrong body.

Hormonal causes

Besides neuroanatomical factors, there are other influences that determine gender. A study published in the Journal Adolescent Health examined the association between hormones and the onset of trans-

genderism [8]. Transgender males and females aged 12 to 24 were included in the study. Researchers measured several hormone levels, including testosterone and estrogen. Since the findings were normal for the sex identities they were assigned to at birth, this would suggest that there is nothing 'wrong' with the hormone levels in transgender people. However, this particular study only looked at the hormone levels at the ages between 12 and 24. It is still unsure if variations in prenatal hormones or hormone levels before puberty have something to do with the feeling of having the body of the wrong sex. Unfortunately, there is no research concerning the difference in hormone levels before the age of 12 between transgender people and cisgender people. Executing such a study would be troublesome because it would require predicting whether a person would decide to change gender or not.

Experimental studies where hormones have been manipulated in a wide variety of mammalian species, show the role of testosterone in early development (prenatally or neonatally). Treating young female rodents with testosterone leads to decreased female-typical and increased male-typical behaviour while castrating male rodents leads to female-typical behaviour. These hormonal manipulations do not only lead to changes in behaviour, but also lead to neural changes in the brain in which the brain becomes more similar to the opposite sex [9]. Manipulation of estrogen levels, by removing the ovaries of female animals, does not have the same effects as manipulation of testosterone levels. The magnitude of the effect of testosterone depends on the phase of development of the animal. In one phase the animal is more sensitive to a hormone than in the other phase. And these sensitive periods can even differ between genders, as is examined in rats [9]. The link between testosterone levels in early development and gender behaviour might give more insight into the existence of gender related issues like sexuality and transgenderism. However, examining this would be problematic due to the unethical aspect of supplying hormones experimentally to pregnant women to test these hypotheses.

What can be studied, however, is the sexual behaviour of children with congenital hormonal imbalances such as congenital adrenal hyperplasia (CAH), which leads to an increase of prenatal androgen excess. A study published in the *Journal of Sex Research* studied the difference in core gender identity, sexual orientation and recalled childhood gender role behaviour between females and males with and without CAH [10]. No differences were reported between males with CAH and unaffected males. On the other hand, the females with CAH showed recalled male-typical play in childhood correlated with reduced satisfaction with the female gender and reduced heterosexual interest in adulthood. Although prospective studies are needed to confirm this, these results suggest that girls with CAH who show the greatest alterations in childhood play behaviour may be likely to develop a bisexual or homosexual orientation as adults or will be dissatisfied with their natal gender. This study supports the hypothesis that testosterone plays a role in critical phases of early development and thereby might have an influence on the sexual orientation and gender identity.

Environmental factors

Neuroanatomic and hormonal factors are possible somatic causes of transgenderism, but could environmental factors cause transgenderism as well? Unfortunately, it is nearly impossible to find any studies about possible environmental factors leading to the onset of transgenderism. A cohort study about this subject is difficult because it cannot be predicted whether someone is transgender. By that, it is necessary to recruit a large cohort and follow them for a long period, which would both be very expensive and extremely troublesome. A good retrospective study also needs a large cohort and allows for recall bias.

There is little research about a possible relation between transgenderism and environmental factors, but we have some hypotheses of our own. The first hypothesis is based on current knowledge on the relation between sexual orientation and environmental factors. Pre-homosexual children show more gender non-conforming behaviour on average than pre-heterosexual children [11]. It seems as if the difference in child behaviour is a result of homosexuality, but perhaps when a child has parents that support the behaviour of the opposite sex, this could lead to homosexuality. This is a really fragile hypothesis since we have to assume that the onset of homosexuality and transgenderism are very similar to each other. In addition, there are many cases that undermine this hypothesis [12-14]. An example is the David Reimer-case: David Reimer was a boy who accidentally lost his penis during surgery and was reassigned to live as a female by his social environment, making him and his cisgender twin brother perfect for research [15]. His twin brother with the same genetics as David served as the ideal control. Despite all the treatments David was given to live as a girl, he never felt like he was one. When his father finally told the truth about his gender, he underwent surgery to undo the caused damage. There is no happy ending to this sad story, since David and his brother both committed suicide, probably due to their traumatising youth.

Like the previous hypothesis, the second hypothesis is also based on the assumption that there are similarities between homosexuality and transsexuality. Certain factors are associated with an increased odds for developing homo-romantic feelings. For men, these factors include having older mothers, divorced parents, absent fathers and being the youngest child. For women, maternal death during adolescence and being the only or youngest child or the only girl in the family are associated with an increased change for homosexual romantic feelings [16]. Hypothetically, there might also be such factors associated with transgenderism.

Like mentioned above, childhood behaviour and certain factors could play a role in the cause of transgenderism. Unfortunately it is very difficult to relate environmental factors to a future outcome unless the coherence between the factors is profoundly present.

Conclusion

We looked at three dimensions that could play a role in the onset of transgenderism: neuroanatomical, hormonal and environmental factors. Firstly, significant neuroanatomical differences exist between men and women, but these only seem to become apparent from adulthood on. This finding is contrary to the observation that transgenders seem to feel at a young age that they were born with the wrong sex. This suggests that the neuroanatomical differentiation between genders might be the result of an unknown factor rather than the cause of transgenderism itself. In addition, it is unlikely that an imbalance in hormone levels influences gender identity, since the hormone levels of transgenders before any hormone treatment show no difference with people that were assigned the same sex at birth. However, there are clues that indicate that prenatal or neonatal hormone levels are involved in the onset of transgenderism. Finally, the role of environmental factors was also discussed, but there is still insufficient quality research to draw any conclusion on this topic. All in all, researching the cause of transgenderism and gender identity is extremely complex, but hopefully new research will shed some light on the mechanisms behind gender.

References

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EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during the bachelor!

We challenge you!

Question 1

Systemic Lupus Erythematosus (SLE) is an autoimmune disease which is characterized by the presence of autoantibodies against DNA, histones and a complex consisting of DNA and histones. Follicular helper T (T_{fh}) cells provide help to anti-DNA-specific autoreactive B cells.

The autoreactive B cells can receive help from T_{fh} cells by presentation in their MHC class II of ...

- A. Only histone peptides
- B. Only DNA fragments
- C. Histone peptides in a complex with DNA

(Module Q4 Attack and Defence 2017)

Question 2

Immunodeficiencies lead to reduced resistance to pathogens. Which part of the immune system is deficient in people who have recurrent severe respiratory tract infections?

- A. Immunoglobulins
- B. Macrophages
- C. T cells

(Module Q4 Attack and Defence 2017)

The answers to these questions can be found on page 12 in this journal.